REMARKS

I. Status of the claims and application

Claims 1, 5-13, and 56-62 are pending. Claims 3, 4, and 14 have been cancelled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of those claims in one or more continuing applications. Claims 1, 9, 10, and 12 have been amended. Claims 60, 61, and 62 have been newly added.

Claim 1 has been amended to clarify that the claimed pharmaceutical composition comprises (A) an arsenic sulfide compound that is substantially free of arsenic impurities and (B) a pharmaceutically acceptable carrier. Basis for this amendment is derivable from page 9, lines 9-10; page 18, lines 25-26; page 18, lines 1-3; and the headline of Section 6.1 on page 18, which states that the invention encompasses a process for producing arsenic disulfide that is substantially free of arsenic trioxide. These parts of the specification make clear that arsenic trioxide is an arsenic impurity. Hence, the present disclosure teaches that the ore from which arsenic trioxide is removed is also treated to remove "*other* impurities" (emphasis added), *i.e.*, non-arsenic impurities.

Claims 9 and 10 have been amended solely to correct their claim dependencies. The Examiner suggested deleting "seman" in claim 10 for "semen." The word "seman," however, (as in "seman platycladi") is a well-accepted term of art that refers to a seed of the medicinal herb, *Platycladus orientalis* (*L.*) *Franco*. Accordingly, Applicant has not amended claim 10 in the manner proposed by the Examiner.

Claim 12 has been amended to delete arsenic trioxide ("As_2O_3"), solely for the purpose of clarifying the claims and expediting prosecution.

New claim 60 further qualifies the hematological cancer of claim 1 as any one of a variety of cancers. New claim 61 incorporates the subject matter of original claim 3 and further limits the composition of claim 1 as being formulated in such fashion that it is suitable for oral delivery. New claim 62 further qualifies the arsenic impurity of claim 1 as arsenic trioxide, for the reasons provided above.

II. The Office Action

At the outset, Applicant notes that the Office Action is "responsive to communication(s) filed on 07 August 2003," *i.e.*, responsive to Applicant's Preliminary Amendment. The most recent communication that Applicant filed with the Office, however, was a Supplemental Preliminary Amendment on September 16, 2003 (USPTO date-stamped postcard is enclosed herewith), in which claims 1 and 3 were amended and claims 58 and 59 were added. It does not appear that these amendments were taken into consideration when the Office Action was prepared, but Applicant has included the language of those prior claim amendments in the present Listing of Claims.

Applicant responds in this paper to each of the following Office rejections:

i. Claims 1-5, and 14 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Yang *et al.* (CN 1061908).

ii. Claims 1-8 and 11-13 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Ellison *et al.* (USSN 2002/0183385).

iii. Claims 56 and 57 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ellison, *supra.*

III. Overcoming the Office's Rejections

i. Yang describes only a mixture of realgar and active ingredients for treating cervical- and skin cancers, but says nothing of an arsenic sulfide compound, substantially free of arsenic impurities, for treating hematological cancer

The Examiner rejected claims 1-5, and 14 under 35 U.S.C. § 102(b) as allegedly anticipated by Yang *et al.* (CN 1061908). The Examiner characterizes Yang as "an anticancer drug comprising arsenic trioxide plus realgar (arsenic sulfide) plus a carrier (resin or alunite)." Office Action at page 2.

In fact, Yang does not teach an arsenic sulfide compound that is substantially free of arsenic impurities, such as arsenic trioxide, for treating hematological cancer (claim 1) or any of the hematological cancers recited in claim 60. Instead, Yang teaches a "pulverized"

mixture of unpurified realgar ore, arsenic trioxide, alunite, and *Commiphora* myrrha resin. Realgar is not equivalent to a purified preparation of arsenic sulfide that is substantially free of arsenic impurities, such as arsenic trioxide. Indeed, realgar is well known to contain impurities such as stones, minerals, and arsenic trioxide.

Similarly, *Commiphora* myrrh is not equivalent to "seman platycladi" because *Commiphora* myrrh is a composition of essential oils, water-soluble gums and alcohol-soluble resins. Its major analgesic constituents are sesquiterpenes, especially, furanoeudesma-1,3-diene. "Seman platycladi," on the other hand, connotes a seed of the medicinal herb, *Platycladus orientalis* (*L.*) *Franco* which can be ground for use as an excipient.

In contrast to claim 1, therefore, Yang's composition is *not* substantially free of arsenic impurities. Accordingly, the present claims are not anticipated by Yang *et al.* and Applicant respectfully requests that the Examiner withdraw this rejection.

ii. The present claims are not anticipated by Ellison because Ellison does not teach treating a hematological cancer with an arsenic sulfide compound that is substantially free of arsenic impurities.

The Examiner rejected claims 1-8 and 11-13 as allegedly anticipated under 35 U.S.C. § 102(e) by Ellison *et al.* (USSN 2002/0183385). The Examiner characterizes Ellison as "a composition comprising one or more arsenic compounds ... in a carrier ... to be used in cancer treatment of mammals" (Office Action at page 3).

Yet Ellison is concerned with "treating solid tumors," *i.e.*, with treatment of cancers of a body tissue. There would have been no basis *a priori* for generalizing from such cancer treatment to dealing with a cancer of the blood, bone marrow, or lymphatic system, *i.e.*, a "hematological cancer," as recited. Ellison himself recognizes this distinction, noting that "there are a plethora of different types of cancers, each of which requires a unique treatment protocol" (page 3, paragraph 24).

To this end, Ellison concluded that arsenic *trioxide* can be used to treat a broad range of cancers, specifically, "non-small cell lung cancer, colon cancer, central nervous system cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer" (page 12,

paragraph 102), but concludes nothing about the treatment of a hematological cancer with arsenic *sulfide*. Furthermore, in contrast to claim 1 of the present invention, Ellison does not contemplate the use of an arsenic sulfide compound that is *substantially free of arsenic impurities*, such as arsenic trioxide. To the contrary, Ellison's anti-cancer agent specifically comprises arsenic trioxide. Thus, for at least these reasons, Ellison does not anticipate the present claims and Applicant, therefore, respectfully requests that the Examiner withdraw this rejection.

iii. Claims 56 and 57 are not rendered obvious by Ellison because the prior art (a) did not identify arsenic sulfide as an anti-cancer agent, and (b) would have deemed it non-sensical to reduce the amount of arsenic trioxide in a pharmaceutial because arsenic trioxide was known to be an effective anti-cancer agent.

The Examiner rejected claims 56 and 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ellison, *supra*. According to the Examiner, Ellison "teaches all that is recited in claims 56 [and] 57, except for the composition comprising the instant amount of arsenic sulfide. It would have been obvious ... to determine the optimum amount of arsenic sulfide" (Office Action at page 3). The Examiner asserts that "[O]ne would have been motivated to do this in order to develop a composition that would have been most effective in treating cancer" (Office Action at page 3).

Claims 56 and 57 qualify the pharmaceutical composition of claim 1 as containing less than 0.15% and less than 0.1% of arsenic trioxide, respectively. Contrary to the Examiner's reasoning, the skilled artisan would not have been motivated to *reduce* the amount arsenic trioxide to such levels, because the skilled artisan would have known that arsenic trioxide was a well-documented, anti-cancer agent. Thus, it would have been paradoxical for the skilled artisan to reduce, in a pharmaceutical composition, the quantity of a substance that was known to be effective in treating cancer. Accordingly, he would not have been motivated to reduce the amount of arsenic trioxide to make Ellison's arsenic sulfide composition "substantially free of arsenic impurities."

Corroborating this lack of motivation is the skilled artisan's understanding that arsenic sulfide was a harmful, if not poisonous, substance. The skilled artisan would have been aware that since the early 1970s, only arsenic trioxide had been considered a suitable

anticancer agent (Zhu *et al.*, Nature Reviews Cancer 2(9): 705-13, 2002). Accordingly, the perceived toxicity (see following subsection) and intermediate nature of arsenic ores, *i.e.*, their use as combustible intermediates for producing As_2O_3, likely led away from their use as anticancer medicaments alone.

Before April 24, 1998, which is the effective filing date of the present application, there was nothing in the art to suggest purifying arsenic sulfide from a natural ore and then administering it to treat cancer, with or without an additional, therapeutic excipient. In 1985, for example, Pershagen & Bjorklund, Cancer Lett. 27(1): 99-104 (1985), found that calcium arsenate "is tumorigenic" and that "the evidence is inconclusive for arsenic trisulfide" (abstract appended). Similarly, a "human carcinogenicity of arsenic" study reported by Tinwell *et al.*, Environ. Health Perspect. 95: 205-10 (1991) (abstract appended), prompted the conclusion that "the natural ore orpiment (principally As_2S_3) was *inactive* despite blood level of arsenic of 300 to 900 ng/mL in treated mice" (emphasis added). Li *et al.*, Zhongguo Zhong Yao Za Zhi 22: 327-9 (1997) (abstract appended), characterized realgar and its sublimates as "poisonous" drugs.

Substantiating this understanding is a recent publication co-authored by the inventor. Thus, Lu *et al.*, Blood 99(9): 3136-43 (2002), reiterated that "realgar as mined" can produce a variety of "toxic effects," especially since different preparations of ore probably would result in different purities of As_4S_4 content. See "Discussion" at page 3142, and page 7 of the present specification, at lines 16-25.

In fact, Dr. Lu notes that although realgar was in common use heretofore, it was actually "employed with several herbal drugs containing hundreds of components." In other words, many putative active ingredients existed in any one preparation. It would not have been possible, therefore, to discern a medicinal affect specifically attributable to realgar, let alone to arsenic sulfide. Since medical efficacy had been attributable to the combination of various amounts of various different active ingredients, therefore, it would not have been possible for the skilled artisan to determine *any* amount of an arsenic sulfide compound, substantially free of arsenic impurities, that was effective in treating hematological cancer. Furthermore, as discussed above, he would have had no motivation to *remove* arsenic trioxide from the arsenic sulfide compound.

Finally, Ellison taught that each cancer requires "a unique treatment protocol" (page 3, paragraph 24), so the skilled artisan would have understood that not all cancer treatment strategies are fungible. Therefore, contrary to the Examiner's assertion, Applicant believes that before the present invention, no arsenic sulfide compound, substantially free of arsenic impurities had ever been categorized as effective against any hematological cancer when used in isolation from its natural ore. For at least these reasons, Applicant asserts that claims 56 and 57 are not rendered obvious by Ellison and respectfully request that the Examiner withdraw this rejection.

IV. Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 22 April 2004 By S. A. Bent

FOLEY & LARDNER
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768